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Published in:
ESMO Open

DOI:
[10.1136/esmoopen-2019-000612](https://doi.org/10.1136/esmoopen-2019-000612)

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Lassen, U. (2019). How I treat NTRK gene fusion-positive cancers. *ESMO Open*, 4(Suppl. 2), [e000612].
<https://doi.org/10.1136/esmoopen-2019-000612>



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To cite: Lassen U. How I treat *NTRK* gene fusion-positive cancers. *ESMO Open* 2019;4:e000612. doi:10.1136/esmoopen-2019-000612

Received 6 October 2019
Revised 4 November 2019
Accepted 6 November 2019

ABSTRACT

NTRK fusions are found at low frequencies (commonly <1%) in a range of common tumour types and at high frequencies (up to or greater than 90%) in rare cancer types (secretory breast carcinoma, mammary analogue secretory carcinoma and infantile fibrosarcoma). The fusions typically occur in a mutually exclusive fashion with other strong mitogenic drivers, and it is of significant importance to identify patients in order to offer transformative treatment with TRK inhibitors. Larotrectinib or entrectinib have resulted in fast and durable response with few and reversible adverse events. Even though on-target resistance may occur, second generation TRK inhibitors are in development and have shown promising activity. Diagnostic strategies must be applied, considering available assays and specific tumour types.

INTRODUCTION

Several chromosomal rearrangements in tumour cells resulting in somatic gene fusions encoding a tyrosine kinase have been identified and such gene fusions may function as tumour drivers. A number of tyrosine kinase inhibitors (TKIs) have been approved, including TKIs targeting *ABL*, *ALK* and *ROS1* fusions.^{1,2} Pivotal studies have confirmed that these agents are superior to chemotherapy in patient harbouring these fusions.

The neurotrophic tyrosine kinase receptors, TRKA, TRKB and TRKC function as receptors for neurotrophins, regulating several aspects of neuronal development and function.³ These receptors are encoded by the *NTRK1*, *NTRK2* and *NTRK3* genes, and oncogenic fusions may occur in any of the three *NTRK* genes, located on the human chromosomes 1q23.1, 9q21.33 and 15q25.3, respectively. The fusion transcripts encode a constitutive active tyrosine kinase domain, comprising the N-terminus of the fusion partner joined to the C-terminus of the TRK protein.⁴

TKIs targeting TRK are novel therapeutic approaches for the treatment of patients with tumours harbouring *NTRK* gene fusions.

FREQUENCY OF *NTRK* GENE FUSIONS

NTRK gene fusions are rare in common solid tumours with a frequency of <1%, but occur more frequently in some rare paediatric and

adult tumour types, with a frequency of up to 100% in infantile fibrosarcoma and secretory breast cancer^{5,6} (table 1). The fusions are more common in the *NTRK1* and *NTRK3* genes, and less frequent in *NTRK2*, and over 60 different 5' partner genes have been reported.⁵

TRK INHIBITORS

Larotrectinib is a highly selective, orally administered inhibitor of TRKA, TRKB and TRKC, with IC₅₀ values in the range of 5.3–11.5 nM.⁷ Safety and activity data have been obtained from patients treated with larotrectinib across three studies: an adult phase I trial, a paediatric phase I–II trial (SCOUT), and the adult and adolescent phase II basket trial (NAVIGATE). A total of 159 patients have been evaluable for response. Response rates of >75% have been reported independent of tumour type, age, *NTRK* gene and fusion partner. Responses are durable with a median duration of response (DoR) of 35.2 months, median progression-free survival (PFS) of 28.2 months and a median overall survival (OS) of 44.4 months.⁸ A total of 260 patients were included in the safety population and adverse events (AEs) were generally mild and transient. The most frequently observed AEs were fatigue, cough, elevated liver function tests, constipation, nausea and dizziness. Dose reduction due to AEs occurred in 8% of both overall patients (22/260) and dose discontinuation due to treatment-related AEs occurred in 6 (2%) patients.

Entrectinib is an orally administered small molecule inhibitor of TRKA, TRKB, TRKC, ROS1, ALK, JAK2 and ACK1 kinases, with IC₅₀ values for the TRK kinases of <5 nM.⁹ Three clinical trials have studied safety and activity of entrectinib: two phase I trials (ALKA-372-001 and STARTRK-1) and the ongoing phase II basket trial STARTRK-2. Response rates by blinded independent review was reported from 54 patients with *NTRK* fusions and the overall response rate (ORR) was 59.3% with complete remission in 7.4%. The median DoR was 12.9 months, median PFS was 11.8 months and the median OS was 23.9

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Table 1 Prevalence of NTRK fusion-positive cancers

Tumour types	Prevalence (%)
Appendiceal cancer	2/97 (2)
Cholangiocarcinoma	1/28 (4)
Colorectal cancer	13/346 (4)
Colorectal cancer dMMR	10/13 (76.9)
Melanoma	1/374 (0.3)
Glioblastoma	3/115 (3)
Head and neck cancer	2/411 (0.5)
Infantile fibrosarcoma	2/4 (50)
Low-grade glioma	2/461 (0.4)
Lung adenocarcinoma	3/91 (3.3)
Mammary analogue secretory carcinoma	2/3 (66)
Papillary thyroid carcinoma	4/33 (12)
Paediatric high-grade glioma	28/127 (22)
Polycystic astrocytoma	3/96 (3)
Secretory breast cancer	12/13 (92)
Spitzoid melanoma	23/140 (16)

Modified from Kheder and Hong.⁶
dMMR, deficient mismatch repair; NTRK, neurotrophic tropomyosin receptor kinase.

months.¹⁰ The safety population included a total of 355 included in the three trials. The safety profile was similar to larotrectinib and most adverse events were grade 1–2 and reversible.

Both larotrectinib and entrectinib are able to penetrate the blood–brain barrier and intracranial response seems to be similar to overall response rates.

RESISTANCE

Even though many patients experience long-term DoR treatment with TKIs may lead to acquired resistance and acquired on-target resistance mutations have been reported in patients with progression during treatment with receiving entrectinib or larotrectinib. Biopsies from such patients have identified one or more kinase domain mutations affecting the *NTRK* gene, leading to sterically change the drug-binding site decreasing the inhibitory properties and potency. These include amino acid substitutions involving solvent front mutations, gatekeeper mutations and mutation in the xDFG domains, which is similar to those described for resistance mutations in other classes of kinase inhibitors. Second-generation TRK inhibitors have been developed to overcome these mechanisms of resistance, like Loxo-195 and repotrectinib.

Recently, off-target mutation have been identified as genomic alterations converging to activation of the mitogen-activated protein kinase (MAPK) pathway, as cases with MAPK pathway-directed targeted therapy alone or in combination with TRK inhibition have been able to re-established disease control.¹¹

TESTING FOR NTRK FUSION

Several approaches that may be used to identify gene fusion in patient samples, including immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH), reverse-transcriptase PCR (RT-PCR) and both DNA-based and RNA-based next-generation sequencing (NGS). FISH or RT-PCR may be used when specific well-known fusions are suspected, which may be the case for *ETV6-NTRK3* fusion in secretory breast cancer. However, >30 different fusions have been identified with three *NTRK* genes and multiple 5' *NTRK* gene fusion partners have been identified. Consequently, using FISH probes for each *NTRK* gene would require three separate FISH assays per patient sample. IHC has been proven highly sensitive and specific¹² for the detection of *NTRK* fusions and pan-TRK IHC is a valuable tool to identify *NTRK* expression. The advantages are the high sensitivity and specificity, the low cost and the fast turnaround time. However, the test may be false positive as it detects only transcribed and translated fusion proteins. DNA-based NGS is able to detect *NTRK* fusions; however, fusions involving *NTRK2* and *NTRK3* with large introns may be missed. Due to chimeric nature of the fusion transcripts, RNA sequencing is the optimal method for the de novo detection of transcribed fusion genes, either as whole transcriptome RNA sequencing or targeted RNA sequencing. Sequencing libraries targets known fusion exons in multiple oncogenes including all of the three members of the *NTRK* family.¹³

STRATEGY FOR TESTING

Different diagnostic strategies must be applied for certain rare tumours with a high incidence of *NTRK* gene fusion events and more common tumour where the incidence is <1% of cases.

In rare cancers, *NTRK* fusion may be pathognomonic and be confirmed by FISH, whereas screening strategies may be used for common tumours. An ESMO working group has published a proposal using IHC to screen when NGS is not readily available, with RNA-based RNA as a reference for confirmation (figure 1).¹³

The fusions typically occur in a mutually exclusive fashion with other strong mitogenic drivers, that is, genetic alterations affecting the most common driver genes belonging to the MAPK signalling pathway (Kirsten RAS virus (KRAS), Neuroblastoma RAS viral oncogene homolog (NRAS) and serine/threonine-protein kinase B-Raf (BRAF)). In lung cancer, *NTRK* fusion may be suspected in non-smokers without other activating genomic alteration after failure of standard of care. In colorectal cancer, it has been suggested that the fusions are more frequent in patients with deficient mismatch repair (dMMR) genes without *BRAF* or *KRAS* mutations, and such patients may be less responsive to checkpoint inhibitors.¹⁴

CONCLUSION

Finding patients with *NTRK* fusion is difficult, as this molecular aberration is rare in common cancers and

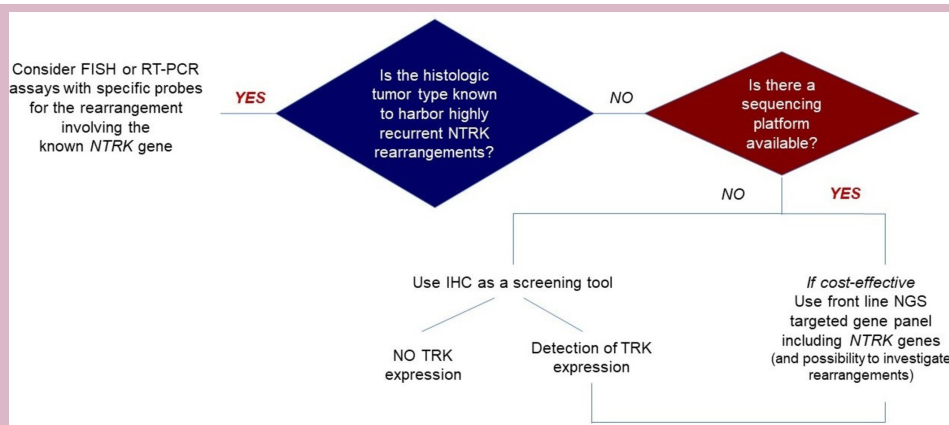


Figure 1 NTRK fusion detection: the ESMO proposal.¹³ FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; NTRK, neurotrophic tropomyosin receptor kinase; RT-PCR, reverse-transcriptase PCR

frequent only in rare cancers. However, it is important to consider testing patients without other activating mutations. The TRK fusions are oncogenic and patients may have failed standard of care. Treatment with emerging TRK inhibitors like larotrectinib and entrectinib may be transformative, leading to fast and durable responses and few adverse event.

Contributors I have written the paper alone without any other contributors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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